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Research Paper

# Primary adenocarcinoma of the appendix: Experience at La Paz University Hospital of Madrid (1967–2014)

Miguel León Arellano [a], Yannko González-Domínguez [a], Fernando Molina-Ortiz [b], María Alexandra Heras Garceau [a], Ramón Cantero [a], José Antonio Rodríguez-Montes [a,*]

[a] Department of General and Digestive Surgery, "La Paz" University Hospital, Madrid, Spain
[b] Department of Pathology, "La Paz" University Hospital, Madrid, Spain

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ABSTRACT

**Background:** Primary adenocarcinoma of the appendix (PAA) is a rare tumor, and it represents 0.03% of all appendiceal pathology. Diagnosis is made during histopathological study in patients with acute appendicitis.
**Objective:** This study aimed to present our experience in this pathology.
**Methods and Materials:** Retrospective study of all patients with acute appendicitis (AA) at University Hospital La Paz of Madrid, during 47 years (1967–2014). We studied age, gender, preoperative diagnose, surgery, histopathology, evolution and survival rate.
**Results:** There were 44 patients with mean age 60.3 years (32–91) with PAA; 25 (47%) were male. The most common preoperative diagnosis was AA in 29 cases (66%), followed by right lower quadrant plastron in 12 cases (27%). AA coexisted in 12 cases (27%). The first surgery was an appendectomy in 32 patients (73%) and right colectomy in 12 (27%). In 32 patients who had an appendectomy, a right colectomy was done between 2 and 5 weeks after first surgery. 30 cases (68%) were well differentiated mucosecretor adenocarcinoma. In 37 cases, tumoral invasion affected serous layer without lymph node affection. 12-year survival rate was 59%. Mean follow up time was 8.2 years (4 months–32 years).
**Conclusions:** PAA is a rare tumor, and in our series it represented 0.01% of 53,019 appendectomies. Preoperative diagnosis was unusual. Clinical presentation was similar to appendicitis. Elective treatment was right colectomy.


## 1. Introduction

Primary adenocarcinoma of the vermiform appendix are rare tumors and are frequently diagnosed incidentally at histologic assessment of the surgical specimen following appendectomy for suspected or diagnosed appendicitis. Neoplasms of the appendix are found in 1% of all appendectomies specimens with a frequency of adenocarcinoma of 0,1% [1]. The incidence of this kind of neoplasm varies from 0,01 to 0,2 per 100.000 persons per year [2] and it constitutes less than 0,5% of all gastrointestinal malignant neoplasms [3,4].

The aim of this paper is to present our experience of adenocarcinoma of appendix at La Paz University Hospital of Madrid.

## 2. Materials and methods

This study involved a retrospective study of all primary adenocarcinomas of appendix at La Paz University Hospital, since January 1967 to December 2014 (47 years). There were no exclusive criteria. Diagnosis of adenocarcinoma was made by a thorough study of the surgical specimens, with identification of surgical proximal circumferential edge, infiltration level and involvement of surgical margins.

Tumor staging was performed according to the classification of Dukes–Astler and Coller; parietal infiltration and lymph node metastasis level were prognostic factors. This classification also applies to colorectal cancer. We followed Wolff–Ahmed's [5] criteria to determine if the origin of the tumor was from the appendix or an infiltration from a cecal neoplasm. The infiltration of the appendix wall was made by complete mapping of the surgical specimen, from intramucosal, submucosa, muscle itself, subserous, serous infiltration to mesoappendix. The base of the appendix was considered as proximal third, and the end as distal; the identified lesions were adscript to their respective third; in those cases where the lesion

* Corresponding author. Department of General and Digestive Surgery, "La Paz" University Hospital, Level 5, Paseo de la Castellana, 261, 28046 Madrid, Spain. Fax: +34 91 5975353.
*E-mail address:* rodriguezmontes@gmail.com (J.A. Rodríguez-Montes).

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was between two thirds, we reviewed the photographic archives to specify the exactly location.

We analyze survival time as a variable given in months, as well as age, gender, localization, tumor size, histologic type, grade of differentiation, infiltration level and the evolution time. We considered alive the dead patients in whom the appendiceal cancer wasn't the cause of death. Statistical study was made by Kaplan–Meyer survival rate.

## 3. Results

During 47 years, there were 53,019 appendectomies performed in our center. Histopathological diagnosis revealed the presence of 44 (0.01%) primary appendiceal adenocarcinomas; a further analysis of the results revealed that 25 cases (57%) were men and 19 (43%) were women. The average age was 60.3 years (32–91 years; SD: 15.04 years). The most common preoperative diagnosis was acute appendicitis in 29 cases (66%), followed by plastron/right inferior quadrant tumor in 12 cases (27%) and appendiceal mucocele in 3 cases (7%). Past medical history and complementary analysis included CBC, thorax and abdominal X-rays, and abdominal CT which was not always performed.

A simple appendectomy was performed in 32 cases (73%) and it was followed by right colectomy between 2 and 5 weeks and in one case in 12 weeks; a primary right colectomy was performed in 12 cases (27%).

Histopathological analysis revealed that the tumor was present at the middle and distal third of the appendix in 32 cases (73%). The macroscopic analysis showed parietal thickening areas with decreased luminal caliber; microscopically the description were: well differentiated muco-secretors adenocarcinomas with a glandular papillary pattern (68%), except in 2 cases (5%), and morphology seal rings in the remaining 12 (27%). In 37 cases (84%) the tumor infiltrated the muscular and serous layers, without lymph node involvement (stage Dukes B2–Astler and Coller).

In 4 cases (12.5%) residual tumor or lymph node metastases were observed in colectomy parts corresponding to the 32 cases (73%) within initial appendectomy. Coexisting acute appendicitis was verified in 12 cases (27%), parietal drilling in 11 (25%) and appendiceal mucocele in 7 (16%) of the operated patients who had a primary adenocarcinoma of the appendix. Tumor size was less than 1 cm in 7 cases (16%), between 1 and 2 cm in 31 cases (70%) and more than 2 cm in 6 cases (14%).

Two patients died in the immediate postoperative period with pulmonary embolism (65 and 91 years old) and 11 died in the period from 4 months to 5.3 years after definitive surgery.

Among postoperative complications there were 2 patients who presented surgical site infection (4.5%); 3 bowel obstruction; 2 acute renal failure; 2 pneumonia; 1 abdominal abscess; and 3 wound dehiscence (6.8%). Two patients received only palliative treatment for peritoneal carcinomatosis; none survived more than four months. Other 4 patients with Dukes C–Astler–Coller received postoperative 5-FU. Global morbidity rate was 27%.

During follow up we observed that there were 3 patients who developed rectal cancer. They were treated with a low anterior resection, radiotherapy and chemotherapy; one of them also developed liver and pulmonary metastases at 9 and 16 months from rectal resection, and he died 4 years after colectomy. One patient had a hysterectomy, oophorectomy and rectal resection for a "pelvic mass" 2 years after colectomy.

Another patient had a bowel resection for an adenocarcinoma recurrence 3 years since colectomy and died 2 years after. One patient was diagnosed with non-Hodkin's lymphoma 3 years after colectomy, and he is alive after 8 years. Mean follow up time was 8.2 years (4 months to 32 years). Overall survival was 86%, 75% and 59.2% for 1, 5 and 12 years.

## 4. Discussion

Primary appendiceal adenocarcinoma is a rare malignancy with 0,12 cases per million diagnosed annually [6,7]. The condition was first described by Berger in 1882 [8]. Appendix carcinomas are usually classified according to histopathological examination into four distinct subtypes with varying frequencies: cystic, colonic, carcinoid, and adenocarcinoid [1,9–11]. Macroscopically there are four forms: ulcerate, vegetative, infiltrative or mixed. Carcinoid subtype is the most common, comprising nearly 90% of all primary appendix tumors.

Mucinous cystoadenocarcinoma is the second most common subtype. Colonic subtype has a 0,082% frequency. The cystic subtype is similar to ovarian adenocarcinoma, thus rupture and dissemination is possible. It has better survival rates compared to colonic subtype.

The colonic subtype originates from a villous or tubular-villous adenoma and it appears as an ulcerated or polypoid tumor [12]. Primary appendiceal cancer is diagnosed in 0,9% to 1,4% of all appendectomy specimens [13].

Acute appendicitis and pelvic or ovarian tumors still are the most common clinical presentation of appendiceal adenocarcinoma [14–18], but rarer presentations include urinary frequency mimicking bladder cancer [19–21], hydronephrosis [22], mimicking Crohn's disease [23], cecal intussusception [24], anemia [25] and Krukenberg tumor of the ovary [26]. In our series 12 patients (27%) presented with acute appendicitis and 19 patients with a palpable right lower quadrant mass, which represents 27% of our patients. Mean age of presentation was in the fifth or sixth decades and sex distribution was equal [27].

Preoperative diagnosis of primary appendiceal carcinoma is invariably difficult since the clinical presentation is usually nonspecific [15]. Therefore, appendiceal carcinoma is always neglected or misdiagnosed [21]. The diagnosis of primary appendiceal carcinoma usually depends on the histopathological analysis following appendectomy or other explorative surgical procedures [27]. Nevertheless, these tumors are seldom suspected before surgery, and less than one-half are diagnosed during surgery [28–30]. Recently, procedures such as intestinal endoscopy, barium enema, and selective ileocolic arteriography have been used for the preoperative diagnosis of carcinoma of the appendix; however, non-established method currently exists.

In accordance with the other published studies [16,21,31], appendiceal neoplasm was established preoperatively in none of our cases. Some authors recommend suspecting the possibility of presenting adenocarcinoma in elderly patients with appendicitis that present inflammatory plastron, lymphadenopathy, or non-inflammatory tissue [32].

One of the most common features of primary adenocarcinoma of the appendix is the tendency to be perforated [15], which occurs in 11 (25%) of our patients (pseudomyxoma is assumed to be a perforated state), and which requires distinguishing the perforation location [11].

The reasons for high incidence of perforation have been attributed to (1) thin muscularis layer in this region of gastrointestinal tract; (2) terminal arterial supply, as opposed to branching arcades of the intestine, and (3) small appendiceal lumen, making it easy to perforate by tumor growth and copious mucinous secretion [33].

Pseudomyxoma peritoneal originates from mucinous appendiceal adenocarcinoma and is characterized by mucinous ascites. Initially, neoplasm obstructs appendiceal lumen; subsequently, appendiceal perforation causes tumor cells to spread into the whole peritoneal cavity. Patients with this condition die from massive tumor load, terminal starvation, or surgical complication from repeated debulking surgery [34].

The significance of tumor histological type remains controversial. The data presented in the literature concerning the prognosis

according to the different histological subtypes are not yet conclusive. McCuster et al. [6] found that 56% of tumors were classified as mucinous appendix carcinoma, 37,6% to the colonic subtype and 6,4% to ring cell subtype. The five year survival rate for all patients was 54,4% and was associated with the stage of disease, the grading and the histological subtype; the same authors reported 5-year survival rates of 44% for tumor with mucinous subtype, 52% for the colonic subtype and 20% for the signet ring cell subtype. Nitecki et al. [29] found a survival rate of 100% for patients with tumors classified as Dukes A, 67% for Dukes B, 50% for Dukes C and 6% for Dukes D carcinomas. Other authors reported that the mucinous histology is the best prognostic factor [7,35], but another study done by Ito et al. [27] claims that mucinous-type adenocarcinoma has poorer outcome. Another study showed no survival difference between colonic-type and mucinous type groups [15]. However, all these analysis share the same problem of small patient numbers so a large multicenter study is still needed for elucidation. The general prognosis seems to be close to that reported for colonic cancer [1,6,27,29].

Preferred surgical treatment is still controversial. While simple appendectomy seems to be sufficient for early, non-invasive carcinomas of the appendix [36], most tumors usually present as advanced invasive carcinomas and a secondary right colectomy is recommended as the treatment of choice [35] between the second and fourth week after appendectomy [12].

Appendectomy is appropriate for the small tumor (pT1), usually found incidentally, measuring less than 2 cm and lacking mesoappendiceal involvement [15]. On the other hand, several clinical studies have demonstrated better survival rate after right colectomy compared to only appendectomy [14,17]. For primary appendiceal tumors greater than 2 cm, involving mesoappendix or base of the appendix, a right colectomy should be considered [36,37]. That is because colonic-type adenocarcinoma can metastasize through lymphatic drainage and a formal right colectomy will solve this problem. For mucinous-type adenocarcinoma with pseudomyxoma peritonei, a right colectomy is the preferred procedure [29].

In our opinion, the criteria of making only appendectomies when there is an "A" stage of Dukes–Astler and Coller [32,38] is not an oncological correct resection, due to the fact that survival rate is higher when a right colectomy is done [17,32], and also because there is a high rate of appendiceal tumoral rests in the colectomy pieces [39]; this happened in 12.5% of our patients. The only situation that appendectomy alone is justified is when the tumor is a villous adenoma appendix limited to mucosa and does not exceed muscularis mucosae and has no vascular infiltration [40,41].

Adjuvant chemotherapy in adenocarcinoma of appendix is not yet established in clinical practice; therefore it is recommended for patients with positive lymph node affection or locally advanced tumors to be treated in accordance with the recommendation for colon cancer. Postoperative adjuvant chemotherapy for stage IV patients shows no survival benefits [20]. However, carcinomas of the appendix frequently shows local infiltration in the surrounding peritoneum with increased risk of locoregional recurrence; for these patients with peritoneal tumor infiltration or peritoneal metastasis cytoreductive surgery in combination with hyperthermic chemotherapy might be an additional therapeutic option [1]. Radiotherapy could decrease the risk of peritoneal local recurrence, in the perforated cases [11], although the results are still poor [5].

Mucinous-type appendiceal adenocarcinoma with pseudomyxoma is a special disease entity. The diffusely scattered tumor cells in the peritoneal cavity usually stay in the peritoneal surface and grow slowly. In the early years, surgeons tried to combat this disease with repeated debulking surgery and intravenous chemotherapy but the results were discouraging [22,42]. In the last years Sugarbaker has developed a definitive cytoreductive surgery with hyperthermic intraoperative intraperitoneal chemotherapy with good results [43]. Nowadays, this concept has become accepted as a feasible option. With conventional debulking surgery, over-all five year survival rates is about 30–50% [20]; however, when cytoreductive surgery and hyperthermia intraoperative intraperitoneal chemotherapy is performed, five year survival rate can be improved to 52–96% according to other authors [42–44]. From the surgical point of view with curative intent, the data of Chen et al. [16] also support that as long as the tumor can be resected radically, there will be survival advantage. To treat primary adenocarcinoma of the appendix many medical institutions around the world are practicing the procedure proposed by Sugarbaker team but many of these centers fail to replicate the safety and survival benefits shown during their initial experience. Clearly, numerous years of experience is required to overcome the initial learning curve before surgeons can appropriately select patients for treatment, perform the procedure safely, and manage the postoperative complications wisely.

The investigation of biological alterations of appendiceal carcinoma have so far reported classic mutations associated with sporadic colorectal cancer including frequent K-ras mutations and rare p53 protein overexpression, and all tumors investigated so far were microsatellite stable [45]. Therefore, the mucinous appendix carcinoma with high grade microsatellite, first described by Komm et al. [1], seems to represent a distinct tumor etiology and might describe a yet unidentified alteration in the DNA repair pathway with possible implications for chemotherapeutic modifications during adjuvant chemotherapy [1].

## 5. Conclusions

Primary adenocarcinoma of the appendix is a rare tumor, representing 0.01% of 53,019 appendectomies in our series. Clinical presentation is quite similar to acute appendicitis. Preoperative diagnosis is difficult, although it may be suspected in some cases. Elective treatment, once diagnosis is made, is right colectomy.

## Author's contribution

MLA, YGD and MAHG acquired and analyzed data; FMO contributed with pathological study; RCC and JARM designed the research, reviewed current literature, discussed the data, wrote and revised the article.

All authors approved final version to be published.

This manuscript has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published.

## Conflict of interest

The authors have declared that no conflict of interest exists.

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